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Exploring the patient experience of digital ulcers in systemic sclerosis

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Short Title: The patient experience of SSc-DU

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Abstract

Digital ulcers are common in patients with systemic sclerosis, affecting over half of patients during the course of their disease. For some patients, digital ulcers occur as isolated phenomena; whereas, for others, digital ulceration is recurrent, and often refractory to intervention. Demonstrating treatment efficacy for digital ulcer disease has typically focussed on clinician opinion of ulcer healing and new ulcer occurrence. Advances in management have improved outcomes which may have had the unfortunate effect of rendering traditional trial endpoints less effective at demonstrating treatment efficacy. Despite recent improvements in management, our work is not complete and digital ulceration remains a major cause of morbidity for many patients with systemic sclerosis. This review shall examine the patient experience of digital ulcers in systemic sclerosis. We shall consider how a detailed understanding of the severity and burden of digital ulceration, aetiopathogenesis, and their impact on emotional health, function, work and social participation might inform the development of novel clinical trial outcomes that can support future advances in the assessment and management of digital ulceration in systemic sclerosis.

Words: 176

Key words: Systemic sclerosis, Digital Ulcers, Patient experience, Health-related Quality of Life, Disability, Function, Impact, Physical symptoms

Introduction

Digital ulcers (DU) are common in patients with systemic sclerosis (SSc), with around half of patients experiencing DUs during their disease course [1–4] and a point prevalence of around 10% [4,5]. Despite the availability of effective treatments to prevent and heal DUs (e.g. phosphodiesterase inhibitors [PDEVi] and intravenous iloprost) [6–8], one third of patients experience recurrent ulceration [9]. SSc-DU are recognised as a prognostic indicator of a more severe disease course, including death [10]. Primary prevention of DU is challenging, particularly with a diagnosis of SSc following the occurrence of DU in many patients. Therefore, to date, our efforts have predominantly focussed on DU healing/secondary prevention.

Clinical trials generally focus on clinician assessment of DU presence and healing but recent negative clinical trials of promising therapies for SSc-DU question the sensitivity of this approach [11]. Patient-reported outcome (PRO) instruments could play a valuable role in supporting future drug development programmes for SSc-DU. The provisional core set of outcome measures for SSc clinical trials recommend assessment of “active digital tip ulcer count on the volar surface” and the use of the DU visual analogue scale (VAS) subscale from the Scleroderma Health Assessment Questionnaire (SHAQ), which asks patients to consider the extent to which DU have “interfered with your activities?” [12]. Global assessments of pain, function and health-related quality of life (HRQoL) using legacy PRO instruments are also used in SSc-DU clinical trials. However, these tools may not capture important patient experiences specific to DU and/or have their impact attenuated through broader experiences of the disease. Devising a specific SSc-DU PRO instrument requires a comprehensive understanding of the biopsychosocial impact of DU experienced by patients and this shall form the focus of this review.

Review strategy

The breadth of this comprehensive review was not amenable to a formal systematic literature review owing to the need to identify and appraise a broad range of sources

including cross-sectional studies, registry analyses, clinical trials and qualitative research methods. The following standardised search criteria were applied within the National Institutes of Health's National Library of Medicine (PubMed) to facilitate the identification of relevant manuscripts (532 citations on 5th April 2018):

(Digital Ulcers) AND (systemic sclerosis) AND (predict* OR work OR site OR qualitative OR experience OR social OR function OR distress OR disability OR symptoms OR experience OR pain OR distress OR social OR quality of life)

The titles and abstracts of journal articles identified from this search formed the mainstay of identifying relevant work, alongside grey searches of manuscripts cited within these articles. When interpreting cross-sectional study findings concerning DU associations (e.g. with legacy instruments assessing pain and HRQoL), it was not always clear whether active DU were present at the time of assessment (as opposed to a history of SSc-DU). Where possible, we shall attempt to define shared patient experiences based on DU activity, burden and aetiopathogenesis, whilst highlighting areas for future research.

Where do SSc-DUs occur?

Hachulla et al[1] recognised three types of DUs: fingertip(ischaemic): extensor(mechanical) and calcinosis-associated (related to mechanical and inflammatory phenomena). In general, fingertip DUs are believed to occur due to ischaemia, whereas, those extensor aspect-DUs occur from recurrent microtrauma/increased tension from skin sclerosis. Ischaemic DUs commonly occur on the tips of the fingers(Figure 1) and over the extensor aspect (in particular, over the small joints) of the hands. Several studies have found that fingertip DUs are more common than extensor-aspect DUs[13,14]. For example, in the retrospective study by Lambova et al[14], which included 60 patients with SSc, over a follow-up period of between 6 months to 6 years, incident DUs were observed in around a third(n=21,35%) of patients, and with a predominance of fingertip(n=18/21) compared to extensor(n=5/21) DUs; however, both types could be found *simultaneously*. Whereas, in a prospective study, which included 148 patients(15 patients who developed 25 SSc-DUs), the prevalence of both fingertip and extensor DUs was 6%[5].

DUs may also occur less commonly at the base of the nail and along the lateral aspects of the digits. DUs may also occur in relation to underlying subcutaneous calcinosis (Figure 2). In a prospective study over four years which included 1614 digital lesions, around half (48.6%) were DUs [15]. Across the range of digital lesions the index and middle fingers were the most commonly affected [15]. SSc-related DUs were mainly found on the fingertips (55.1%) and extensor aspects (30.6%). Palmar aspect ulcerations were rare (3.3% of all 'pure' DUs) [15]. DUs may also develop in relation to digital ischaemia/gangrene [7,15].

In general, fingertip DUs are believed to occur due to ischaemia, whereas, those extensor aspect-DUs occur from recurrent microtrauma/increased tension from skin sclerosis (Figure 2). Understanding the similarities and differences in the pathogenesis of SSc-DUs could have important clinical and research implications. For example, recent multicentre, placebo-controlled clinical trials [10,56,57], have only included fingertip DUs, presumably as they are believed to be ischaemic in origin, and therefore most likely to benefit from treatment with vasodilatory therapies. However, there are emerging data which could suggest that extensor aspect DUs also share a (potentially reversible) ischaemic component [16]. Indeed, laser-derived tissue perfusion imaging suggests both fingertip and extensor DUs are characterised by an ischaemic core [17,18].

Which patients develop SSc-DUs?

Some studies have reported that SSc-DUs occur more commonly in males [2,3,19–21], whereas, others have not identified gender-related differences [4,22], or have suggested SSc-DU are more common in females [23]. Several studies have reported a higher burden of SSc-DU in diffuse compared to limited cutaneous SSc [14,19,23]. SSc-DUs have been associated with higher skin [1,3,4,20,23,24], including hand and finger score [4] although SSc-DU were unrelated to the extent of skin thickening in the Scleroderma Lung study II [25]. In general, an earlier disease onset [3,4,24], earlier occurrence of the first non-Raynaud's phenomenon SSc symptom [20,23], and younger age have been reported to be associated with SSc-DUs [1]. A number of authors have identified anti-Scl70 antibody positivity as a risk factor [2–4,19,20,23,26]. Data from Digital Ulcer Outcome (DUO), a post-marketing

surveillance register of patients receiving treatment with bosentan, revealed that the first DU in patients with anti-Scl70 occurred approximately 5 years earlier than the those with anti-centromere antibody[27]. Caramaschi et al[24] reported that the presence of joint contractures was associated with DUs, and occurred in patients with diffuse cutaneous SSc and anti-Scl-70 antibody positivity. In one study, patients with RNA polymerase III antibody were more likely to develop DUs over joint contractures compared to fingertip DUs[2].

Delay in vasodilator therapy[1], including iloprost[24], has been associated with SSc-DUs. There is evidence for and against an association with smoking[2,4]. Impaired diffusion capacity[3,4], interstitial lung disease (ILD)[4,20], cardiac involvement[20] including pericardial effusion[23], gastrointestinal including oesophageal involvement[20], and treatment with corticosteroid therapy [24] have each been associated with SSc-DUs. The association between DUs and -pulmonary arterial hypertension (PAH) and scleroderma renal crisis is less certain[4,20].

It is expected that SSc-DUs occur more frequently in colder weather, although few studies have examined the relationship between season and SSc-DU occurrence and some patients experience SSc-DU during Summer, reflecting the severity of micro- and macrovascular disease. One multicentre study from Brazil including 141 patients with SSc, suggested patients living in the colder (subtropical) zone were 5 times more likely to develop DUs compared to those who lived in the warmer (tropical) climate[28].

What is the natural history of SSc-DU?

In the previously described study by Amanzi et al[29], the mean time to healing of 'pure' DUs was 76.2 days and in calcinosis-associated DUs was 93.6 days. Factors associated with increasing healing time included infection, presence of fibrin, perilesional oedema, wet or dry necrosis, bone and tendon exposure, and gangrene. There are no data on whether patients can predict SSc-DUs. This has important implications on the development of new treatment options for intercurrent DUs including novel PRO instruments.

What are the physical symptoms of SSc-DU?

In addition to the physical presence of epithelial denudation that defines SSc-DU, pain is the major physical symptom of SSc-DU. Overall, pain VAS scores are significantly greater in patients with active DU compared to those without[30].

Whilst no qualitative research studies have specifically explored the patient experience of SSc-DU, previous studies examining symptom burden in SSc have acknowledged the impact of ulceration on distal extremity symptoms and function as the following quotation attests:

“..the pain that you felt in your fingers as they were dying was so excruciating that you almost begged to say please cut it off” (reproduced from[31])

Unsurprisingly, a higher burden of DU is associated with higher analgesic requirements[32].

What is the emotional impact of SSc-DU?

Clinical experience suggests SSc-DU are associated with considerable emotional distress although surprisingly few studies have specifically examined the impact of SSc-DU on psychological health. The specific effects of DU on emotional distress did not emerge as a strong theme in qualitative studies examining living with SSc, although not all participants in these broad ranging studies will have experienced DU[33–36].

There is no disease-specific PRO instrument for assessing psychological ill health in SSc. The presence of SSc-DU is associated with higher depression scores assessed using legacy instruments such as the Beck Depression Inventory[37]. In contrast, this study did not identify an association between depression and either skin score, digital loss, severe digital contractures, gastrointestinal disease or pulmonary physiology, highlighting the specific emotional impact of SSc-DU. Similarly, patients self-reporting the presence of SSc-DU were found to have higher Psychosocial Adjustment to Illness Scale(PAIS) scores, although this

association was lost during regression analysis adjusting for other potential confounders [38]. The Hospital Anxiety and Depression Scale(HADS) and Mental Component Summary (MCS) of the Short Form-36 questionnaire(SF-36) have identified inconsistent associations between the presence of active SSc-DU and emotional ill health[39–42]. One study suggested SSc-DU was an important source of body image dissatisfaction in African American patients with SSc[43]. A more thorough understanding of the emotional impact of SSc-DU might facilitate more targeted evaluation of emotional distress in SSc-DU.

Impact of SSc-DU on function

SSc-DU have been identified as one of the disease manifestations affecting fine motor function of the hands in qualitative research studies exploring experiences of patients living with SSc[44] although not all studies exploring activities of daily living in SSc make specific reference to the contribution of DU on functional capacity[36]. A therapist-led assessment of hand function during observed activities of daily living identified a number of functional impairments caused by SSc[45]. Contrary to expectations, it was digital sores (and calcinosis cutis) rather than higher skin scores and tendon friction rubs that had the largest impact on individual patient's ability to grasp and utilise everyday objects[45]. A longitudinal study examining hand function did not reveal any significant deterioration in hand function over 5-years, despite significant worsening of friction rubs, calcinosis and puffy fingers[46]. The findings may reflect a relatively stable prevalence of DU disease over this time course of this study and highlight the importance of DUs on overall hand function[46].

Measuring the functional impact of SSc-DU in isolation has been challenging. The presence of DU might relate to a broader clinical phenotype that can affect function, particularly if function is assessed using legacy instruments developed for other diseases. For example, there are differences in cardiopulmonary physiology in SSc patients with and without a history of DU which could influence domains such as mobility[4,47]. One of the first studies to examine the impact of the DU on function arose from initial efforts to validate the Health Assessment Questionnaire–Disability Index(HAQ-DI) in SSc[48]. A number of clinical features were noted to influence HAQ-DI scores including disease subsets, total skin score, restricted

joint movement such as increased finger-to-palm distance, joint pain and the presence of tendon rubs, but the presence of DU did not appear to influence either the total HAQ-DI score or individual components thereof[48]. Indeed, it was these findings that formed the justification for modification of the HAQ to include VAS for unique aspects of SSc such as DU disease that were not adequately captured using the standard HAQ-DI alone[49]. This could also explain the poor correlation between the DU VAS subscale of the Scleroderma HAQ and both the total HAQ-DI or the UK Scleroderma Functional Score[50]. The SHAQ DU VAS subscale can differentiate between patients with active DU, healed DU and a history of DU but its limited focus on interference with activity restricts the granularity of the data obtained from this single item PRO instrument on the broad and complex domain of functional capacity[49,51].

Analysis of clinical trial data from a large clinical trial of SSc-RP compared outcomes in patients with or without DU disease and suggests a more nuanced assessment of the impact of SSc-DU on hand function is required[30]. The analysis did identify modestly higher HAQ-DI scores (1.03 vs. 0.81, $p=0.02$) in patients with active DU, although a sub-analysis of the individual components of the HAQ-DI was more illuminating with significant differences for grip (1.67 vs. 1.30, $p=0.005$), eating (1.26 vs. 0.90, $p=0.027$) and dressing/grooming (1.31 vs. 0.85, $p=0.0002$) but not for the other domains of the HAQ-DI less obviously influenced by hand function such as mobility[30]. Other studies have also identified associations between the presence of active DU and higher HAQ-DI score[28,38], although one of these studies relied upon “patient-declared” (rather than clinician-confirmed) DU[38]. Noting the discrepancy that exists in agreement amongst Scleroderma specialists regarding the presence of SSc-DU disease[52–54], allowing patients to self-declare the presence of DU could result in misclassification of digital ischaemic lesions and unduly influence associations with other PRO instruments.

Patients with persistent SSc-DU have significantly higher HAQ-DI scores compared to those without a history of DUs[2]. These patients also report higher levels of pain (SHAQ Pain VAS), interference secondary to DU (SHAQ DU VAS) and loss of upper extremity (but not large joint) function[2]. These SHAQ indices are increased further in patients considered to have

“severe” persistent SSc-DU (persistent or recurrent ulcers for 6 months complicated by gangrene, or requiring digital sympathectomy or amputation)[2]. The effects of SSc-DU on function appear to be reversible with a study of an incident cohort of patients with SSc-DU disease identifying significant differences in functional capacity in patients whose DU had persisted or new DU formed at subsequent follow-up (median 2 years) compared to those in which sustained healing of DU had occurred[42]. In contrast, a separate study examining function in a cohort of patients who had experienced ≥ 1 DU within the last year, did not reveal a difference in function between those with active DU at study entry and those without DU using the HAQ-DI alone[41], although pain VAS and Cochin Hand Function Scale (CHFS) were both higher; again suggesting a focus on hand function strengthens associations between DU and disability[41]. Indeed, the multivariate regression analysis examining the factors most influencing CHFS scores in patients with SSc (and a history of DU) identified active DU at study entry as the strongest factor independently associated with CHFS scores[41]. The significant linear relationship between the total number of DU and the CHFS, however, was lost when the analysis was restricted to patients with active DU at study entry, suggesting hand function becomes impaired as soon as 1 DU is present with little additional disability accrued with additional ulceration[41]. Like the HAQ-DI, the CHFS was originally developed for use in arthritis[55]. The relationship between SSc-DU and hand-specific function was not evaluated when the CHFS was initially validated for use in SSc[56]. A subsequent study to validate the Italian version of the CHFS did consider the potential impact of SSc-DU on hand function[57]. Despite the expected effects of DU on hand function, no difference was found between CHFS scores in patients with and without SSc-DU, whereas, significant differences were identified for both the CHFS and HAQ-DI in SSc patients with arthralgia[49]. In contrast, subsequent studies have suggested higher HAQ-DI and CHFS scores in SSc patients with active DU compared to those without[5,40]. The MACTAR, which allows individuals to set their own priorities when reporting functional impairment does not differ between patients with and without SSc-DU, highlighting the diverse and competing causes of disability (and hierarchies adopted by patients rating disability) in SSc[39]. Other studies have also identified higher HAQ-DI scores in patients with active DU but no difference in overall MACTAR scores[40].

As previously described, different forms of SSc-DU are recognised. The HAnd Mobility In Scleroderma (HAMIS) test scores are higher in patients with active DU, irrespective of type, and the authors concluded that studies examining new interventions for SSc-DU could include both types of DU[5]. A modified version of the HAMIS has also been shown to differentiate between those with and without DU[58].

Effective treatment of SSc-DU appears to improve hand function. The RAPIDS-1 trial reported a 48% decrease in the mean number of new DU in patients treated with Bosentan[59]. Whereas changes in the complete HAQ-DI did not differ between treatment arms, a sub-analysis focussing on the domains of the HAQ-DI pertaining to hand function did reveal significant differences between bosentan-treated and placebo-treated patients at 16 weeks with notable improvements in domains concerning dressing/grooming and personal hygiene[59]. The RAPIDS-2 study also identified a significant decrease in the mean number of new DU but did not identify significant differences in disability (or pain) between the bosentan and placebo-treated arms[60]. Seibold and Matucci-Cerinic acknowledged the insensitivity of current measures of hand function with regards to digital tip ulcers as a barrier to drug development programmes[61,62]. A post-hoc analysis of the RAPIDS-1 & RAPIDS-2 data did, however, suggest an improvement in the HAQ-DI score (again particularly concerning components relevant to hand function) in patients without DU compared to those with DU (either persistence or new) at the end of the study suggesting this instrument is moderately responsive to interventions influencing DU burden[63]. Studies demonstrating the favourable effects of PDE5 inhibitors on DU healing have also identified significant improvements in VAS assessments of daily activity[64].

The Hand Disability in SSc-DUs (HDISS-DU) is a newly developed 26-item comprehensive, instrument, derived in part from the CFHS[65]. Data from a qualitative interview study (currently published in abstract form) revealed that the draft HDISS-DU is a comprehensive, content-valid instrument, which captures the impact of SSc-DUs on hand function. Further research is ongoing to fully validate the instrument.

Impact of SSc-DU on health-related QOL?

References to SSc-DUs in qualitative research studies examining symptom burden and quality of life in SSc have generally focussed on physical symptoms of DU pain rather than HRQoL[31,66,67]. Other qualitative research studies exploring HRQoL and educational needs for patients with SSc make surprisingly little reference to DU[33,68]. These studies have generally not reported how many patients within the cohort had experienced SSc-DU, and this could represent inadequacy of the purposive sampling frameworks to ensure a representative cohort.

Again, insight into the possible effects of SSc-DU on HRQoL can be gained from reviewing the relationship between validated generic HRQoL outcome measure and SSc-DU. One study examining the functional impact of SSc-DU also identified differences in the mental (but not physical) component score of the SF-36 instrument for assessing HRQoL[39]. This study also identified higher aesthetic concerns in patients with SSc-DU; perhaps indicating that some of the psychological impact of SSc-DU relates to body image dissatisfaction[39]. Sub-analyses of the SF-36 subdomains (as opposed to composite scores) also identified impairment in mental health and higher bodily pain in patients with SSc-DU[39,40]. Once again, the overall burden of SSc-DU appears relevant. For example, a study examining an incident cohort of patients with SSc-DU identified significant differences in both the PCS and MCS in patients for whom SSc-DU had persisted or new DU formed at subsequent follow-up compared to those with sustained healing of DU[42]. Previous clinical trials have not specifically examined the impact of intervention for SSc-DU on HRQoL although there could be a valuable role for HRQoL measures in clinical trial endpoint models for SSc-DU(Table 1) [59].

Impact of DU on domestic, work and social participation?

SSc has a considerable impact on capacity to work and the need for financial support. Inability to perform community, social, and civic life was the most commonly reported ICF domain by patients asked to prioritise patient perceived disability related to SSc using the McMaster Toronto Arthritis patient preference questionnaire (MACTAR) questionnaire[40].

Work and employment was ranked 4th in the activities limited by the disability of SSc[40]. An early cross-sectional study found that 60.9% of SSc patients were on permanent sick leave and 35.6% receiving disability benefits, with low performance status and myalgia identified as independent factors associated with work absenteeism[69]. Reduced global and hand function are associated with permanent sick leave[69]. SSc-DU directly impact on domestic, work and social participation when hospitalisation for DU management is necessary, removing people from their home and family environment[9,42]. Even when hospitalisation isn't necessary, SSc-DU impacts on work productivity and social participation. SSc-DU are associated with greater limitations in daily activities, greater reliance on others for domestic tasks and greater requirement for external domestic support (paid and unpaid)[40]. However, overall limitations in activities of daily living appeared to be similar in patients with active DU and those with a history of DU suggesting such effects might be resilient to intervention [40]. Furthermore, whilst there was a 59.3% employment rate in those expected to be in the workforce (with 31.8% of patients requiring full disability pension), decreased work productivity appeared to be primarily related to the broader effects of SSc, and no specific differences were identified in work status between patients with and without SSc-DU[40]. A preliminary analysis of the DUO registry identified a relationship between the overall DU burden (number of DUs at enrolment) and greater work impairment, as well as inability to perform daily activities and progressively greater need for paid and unpaid support[32]. Further DU registry analysis confirmed these findings whilst also highlighting the relevance of the overall SSc-DU burden with patients with "chronic DU" (DU present at every follow up visit) reporting higher rates of work impairment, activity impairment, need for paid and unpaid help[9]. A higher burden of DU was also associated, unsurprisingly, with higher analgesic requirements and rates of hospitalisation[32].

Interventional studies have yet to examine the impact of treatments on work or social participation[59] and few studies have addressed the socioeconomic costs of SSc-DU. One attempt estimated the mean per patient per annum cost of SSc-DU to be €23,619, with approximately 10% of the total societal cost of SSc-DUs relating to lost work productivity for patients and/or their caregivers; approximately half of whom remain in employment[70]. Qualitative research studies examining work participation in SSc identified DU as an

important cause of hand pain, but did not provide any specific examples of how DU had interfered with work capacity[71,72]. SSc-DU has been identified as a factor influencing disruption to sexual lives[35].

Implications for current assessment and management of SSc-DU

As previously described the primary end-point in recent clinical trials of drug therapies for SSc-DUs has been based upon clinician opinion, however, the agreement between clinicians with an interest in SSc is poor to moderate at best[52–54].

Existing clinical trial endpoints largely overlook the patient experience of SSc-DU. There are examples from qualitative research studies of patients with SSc using their experiences of DU to guide clinicians on optimal management as highlighted in the following passage:

“I was the one with the ulcers that said let’s try a topical anesthetic.....He’s offering me codeine, which means I can’t function the way I want to function, when really we know exactly where the pain is, I don’t need my whole body numbed down, I need this [points to fingers] numbed down.”(reproduced from[34]).

In the absence of a disease-specific PRO for assessing the severity and impact of SSc-DU, there is currently a reliance on legacy instruments to assess the patient experience of SSc-DU (Table 1). This approach risks the undesirable inclusion of items not relevant to SSc-DU (such as non-hand domains of the HAQ-DI) and the exclusion of items encompassing important experiences of SSc-DU (such as emotional distress and the effects of DU on social participation).

Conclusions

Relatively few studies have examined the patient experience of SSc-DU. Much of our current understanding of the impact of SSc-DU has been derived from cross-sectional studies utilising legacy PRO instruments to assess broader aspects of SSc severity. There is a danger that such instruments might miss the multifaceted patient experience of SSc-DUs, including

The patient experience of SSc-DU

differences between different DU subtypes. Further research is indicated to understand the patient experience of SSc-DU, including to develop PRO instruments to support advances in treatment.

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Figure 1. An ischaemic fingertip DU in a 43-year-old construction worker with limited cutaneous SSc (positive Ro-52 autoantibodies).

The DU was causing considerable pain (SHAQ pain VAS 76/100, despite a global disease VAS of only 55/100), leading to reduced functional capacity (total HAQ score 1.0 despite scores of 0 for reach, walking and rising domains), leading to interference with daily activity (SHAQ DU VAS 88/100) and affecting work participation.

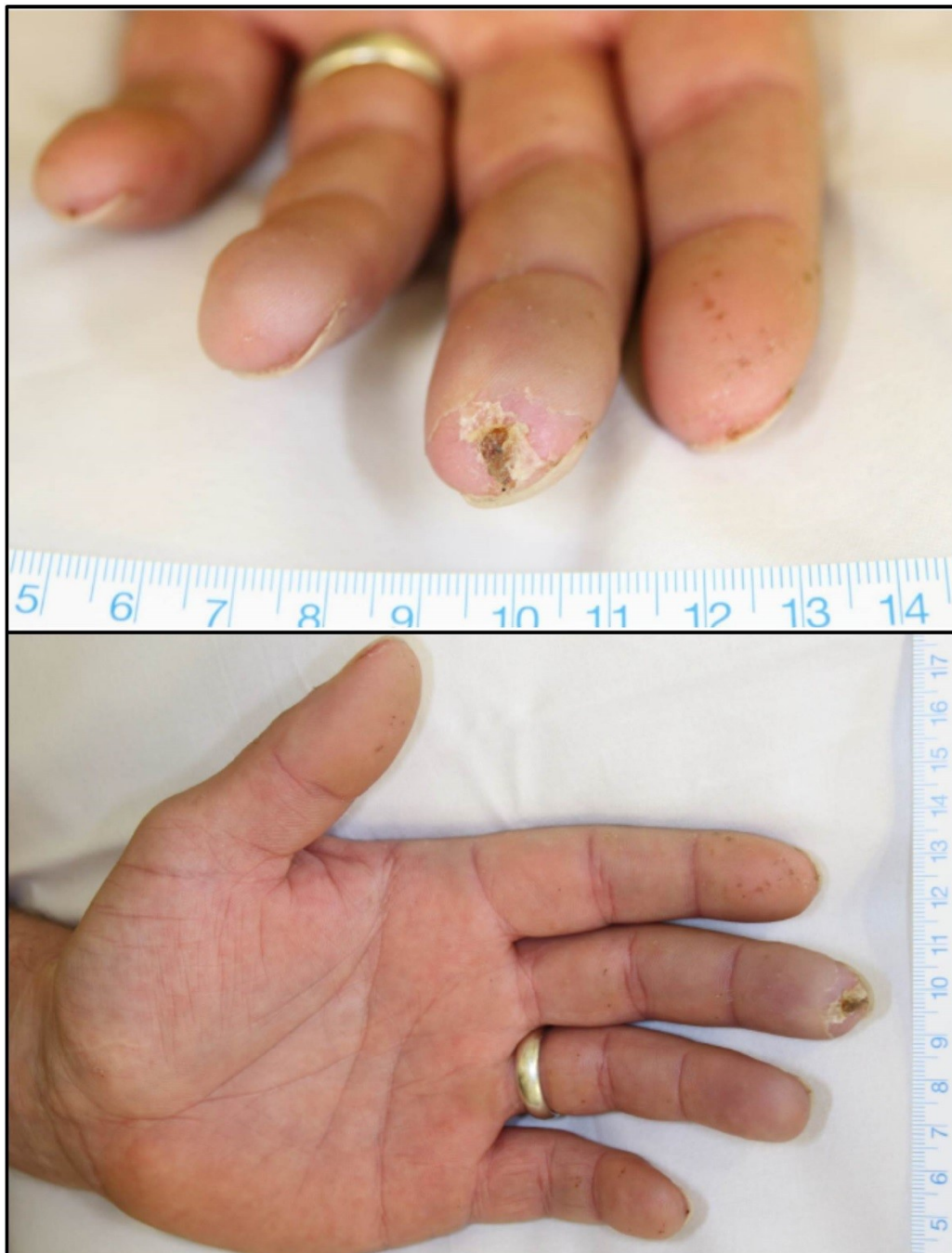


Figure 2. Non-ischaemic cutaneous ulceration in SSc. A. Mechanical and calcinosis-related extensor ulceration in a 49-year-old lady with diffuse cutaneous systemic sclerosis (positive RNA Pol III antibodies) despite treatment with phosphodiesterase inhibitors and endothelin receptor antagonists. B Plain radiograph of the hand demonstrating calcinosis cutis and C. Favourable response following minocycline therapy for calcinosis cutis. Adapted and reproduced with permission from [73].

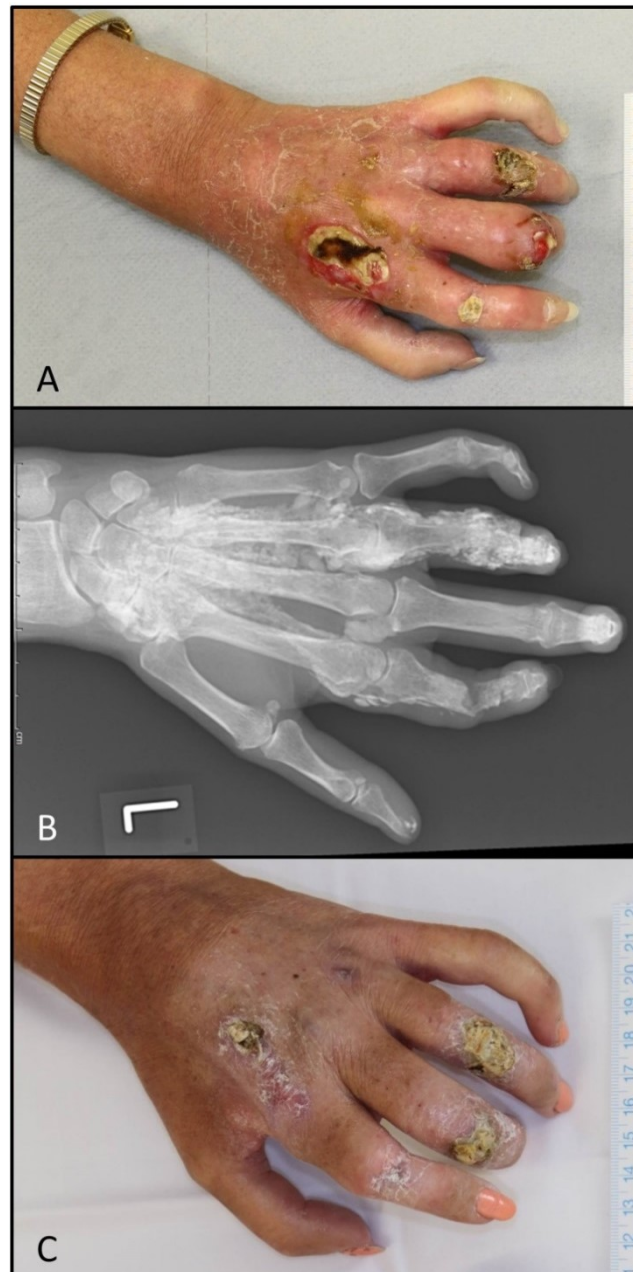


Table 1. Legacy and disease-specific PRO instruments that could be used to assess the impact of SSc-DU in future clinical trials.

CHFS, Cochin Hand Function Scale; HADS, Hospital Anxiety and Depression Scale; HAQ-DI, Health Assessment Questionnaire-Disability Index; SHAQ, Scleroderma HAQ; HAMIS, HAnd Mobility In Scleroderma; HDISS-DU, Hand Disability in SSc-DUs; MCS of SF-36, Mental Component Summary (MCS) of the Short Form-36 questionnaire(SF-36); PAIS, Psychosocial Adjustment to Illness Scale; MACTAR, McMaster Toronto Arthritis patient preference questionnaire

Domain	Legacy instrument	SSc-specific
Function	HAQ-DI	SHAQ DU VAS subscale
	HAMIS	UK Scleroderma Functional Score
	MACTAR	HDISS-DU
	CHFS	
Psychological distress	HADS	
	Beck Depression Inventory	
	PAIS	
	MCS of SF-36	
Pain	Global assessments of pain	SHAQ Pain VAS
HRQoL	SF-36	